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10/518,861	03/21/2005	Kenichiro Kosai	042-301	9980

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,861	KOSAI ET AL.	
	Examiner	Art Unit	
	Maria Leavitt	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED *(35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *37 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12-07-2004* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03-07-2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Detailed Action

Claims 1-38 are pending in the instant application. Applicant's election without traverse of Group I drawn to claims 1-23, 24-29, and 33-36, and election of the following species: a CA as the constitutive strong expression promoter, and a Nkx2.5 as the second gene promoter in the response filed on 04-09-2007 is acknowledged. Claim 35 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected species and claims 37 and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected invention there being no allowable generic or linking claim.

Claims 30-32 were inadvertently left out of a Group. Since claims 30-32 are drawn to kits comprising a first recombinant DNA and a second recombinant DNA and cells transformed with said constructs they will be examined with Group I.

The requirement is still deemed proper and is therefore made FINAL.

Currently, claims 1-34 and 36 are under examination to which the following grounds of rejection are applicable.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed on 24-12-2003 in Japan. It is noticed, however, that applicant has filed a non-translated certified copy of the PCT/JP03/07536 06/13/2003 application.

Claim Rejections - 35 USC § 112

Claims 1-34 and 36 are examined as the related to the elected species: a CA as the constitutive strong expression promoter, and a Nkx2.5 as the second gene promoter.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-34 and 36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

a method of identifying and isolating a differentiated mouse cardiac muscle cell derived from a mouse ES cell by detecting expression of a fluorescence marker whose expression is restrictively activated in said differentiated cell comprising:

(i) Transforming a mouse ES cell with a first DNA construct encoding a fluorescence gene marker operably linked to a strong constitutive promoter, wherein the DNA encoding said marker gene is separated from said promoter by a sequence of DNA which prevents transcriptional control by said promoter over the DNA encoding the marker gene,

(ii) transforming the cell of (i) or a differentiated descendant cell with a second DNA construct comprising a DNA encoding a recombinase-expressing gene operably linked to a Nkx2.5 gene promoter, wherein said recombinase is capable of removing the sequence of DNA preventing transcriptional control in the first DNA construct, and

(iii) monitoring said differentiated cells for sufficient visible level of fluorescent expression for identification of ES-derived cardiac muscle cells and subsequent isolation,

does not reasonably provide enablement for a method of isolating or visualizing a target cell from any embryonic stem cell as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims, when given the broadest possible interpretation, encompass a method for selectively isolating or visualizing any differentiated ES cell e.g., pig, sheep, cattle, rabbit, mink, monkey by transfecting said cells with two recombinant DNA constructs, wherein the first construct comprises a constitutive CA promoter and the second construct comprises a cell specific Nkx2.5 promoter so as to selectively isolate the transfected differentiated cell. Moreover, the instant claims broadly read into any selective marker (e.g. including markers that require an enzymatic reaction for detection) that is expressed so as to selectivity visualize or isolated said transfected target cells. Further, the claims do not indicate how the transfection of a

target cell with two recombinant DNA constructs reflect on the efficacy of the isolation. Thereby, specific issues including isolation and visualization of any transfected embryonic ES cell derived from **any species** able to restrictively activate a recombinase-expressing gene operably linked to the cell specific Nkx2.5 promoter and thus remove the restriction that prevents sufficient expression and visualization of a maker gene under the control of the CA promoter have to be examined and considered for patentability regarding the broadly claimed methods.

The as filed specification teaches in Example 1, differentiation of mouse ES cells into a self-pulsing like cardiac muscle cells after adding recombinant protein of mouse leukemia inhibitory factor (LIF) (p.18, last paragraph). Expression of cardiac muscle-specific genes e.g., Nkx2.5, αMHC, MLC2v was confirmed by RT-PCR (page 19, paragraph 2). ES cell were transfected by electroporation with a first recombinant DNA: pCMV-loxP-Neo- EGFP or pCA-loxP-Neo- EGFP (page 22, paragraph 3) and a second recombinant DNA in the form of a human 5-type adenovirus vector comprising a recombinant Cre gene under the control of a tissue specific Nkx2.5 promoter gene. The specification teaches that strong expression of EGFP was observed by stable transfer of pCA-loxP-Neo-EGFP and excision of a Neo gene held by loxPs after expression of a Cre enzyme under the control of the Nkx2.5 promoter gene (page 28, paragraph 1). Moreover, the specification contemplates the isolation of a cell at different stages of embryonic differentiation (page 31, last paragraph). Additionally, the as filed specification discloses that when EGFP (enhanced green fluorescence protein) is under the control of the Nkx2.5 gene promoter in cardiac muscle cells derived from ES cells, the expression of EGFP is

not sufficient to be visualized with a fluorescent microscope and thus the cells cannot be isolated (page 20, last paragraph).

In so far as the use of the first construct comprising a constitutive CA promoter operationally linked to a EGFP and the second construct comprising a cell specific Nkx2.5 promoter able to sufficiently express a EGFP gene marker in a R1 cell of a mouse ES cell the as filed specification provides sufficient guidance. The specification teaches expression of EGFP under the control of a constitutive strong expression promoter e.g., CA and CMV (p. 7, paragraph 1; page 21, paragraph 2). Differential expression of EGFP was observed in differentiated ES cells with each of the CA and CMV promoters used, with the CA promoter able to induce stronger expression than a CMV promoter (page 27, paragraph 2), indicating tissue-specific activity of constitutively strong promoters in mouse ES cells and mouse primary cardiac muscle cultured cells (p. 42, last paragraph) . Moreover, the as filed specification discloses cell and size specifity of a second DNA promoter gene comprising a Nkx2.5 gene (i.e., promoter region from the initiation of transcription to –9000 bp). Experimental results indicate that longer or shorter regions of said promoter were not able to express a downstream cardiac muscle –specific gene at sufficient levels, thus indicating the specificity of the Nkx2.5 (i.e., promoter region from the initiation of transcription to –9000 bp) for optimal expression of the Nkx2.5 gene (page 15, last paragraph). However, the as filed specification is silent about isolation and visualization of any other species of ES cells other than mouse ES cells. The detail of the disclosure provided by the Applicant, in view of the prior Art, must encompass a wide area of knowledge to enable one of ordinary skill in the art at the time of the invention to practice

the invention without undue experimentation. However, as it will be discussed below this undue experimentation has not been overcame by the as-filed application. Though, the specification teaches selective isolation and/or visualization of mouse ES cells and mouse primary cardiac muscle cultured cells after transfection of said cell with two vectors comprising the a constitutive CA promoter and a cell murine specific Nkx2.5 promoter which allow expression EGFP, the broad aspects of selectively isolating or visualizing a target cell differentiated from an any embryonic stem cell other than mouse is not reasonably enable for the full scope embraced by the claims. Moreover, the use of any marker other than a fluorescence marker is not enable for the full scope embraced by the claims.

At the time of filing, the art teaches that transgenic technology in embryonic stem cells is exclusively known for mice and human embryonic germ cells. In relation to mouse ES cell, Moreadith et al., (1997, J Mol Med pp. 208-216) teaches that gene targeting and transgenic technology in embryonic stem cells is generally limited to the mouse at the present (p. 214, col. 1, paragraph 3). Though several putative ES cells lines had been isolated from hamster, pig, sheep, cattle, rabbit, rat, mink, monkey and humans, the technology is limited to mice (page 214, col. 1, paragraph 3, lines 5-12). Prelle et al., (1999, Cell Tissues Organs, pp. 220-236) brings similar insight into the lack of predictability of using any ES cell in transgenic technology when he states that many embryo-derived cell lines resemble morphologically mouse ES cells, and have the ability to differentiate *in vitro*, but there is no evidence of live born, fertile germ line chimeras in mammalian species other than mouse (page 222, col. 2, paragraph. 1, lines 10-16). In so far a human embryonic pluripotent ES cells, Gearhart et al., (US Patent 6,090,622) teaches human pluripotent ES cells that can differentiate into cell for replacement and/or repair of a

number of tissues (col. 10, lines 22-35) . Thus at the time of filing, the art teaches that embryonic lineages is limited to murine or human ES cells as they develop into totipotent cells.

In relation to the use of cell specific promoters in cardiomyocytes generated from the inner cell mass of mouse blastocyst, the art teaches that is was well known to use cardiac restricted promoters (e.g., Gata4 and Nkx2.5) for expression of a marker gene to isolate a pure population of mouse ES cell-derived cardiomyocytes (Fijnvandraat et al., (J. of Molecular and Cellular Cardiology, 2003, pp 1461-1472). However, the art teaches the unpredictability of using any gene marker to isolate and/or visualize a SC population. For example, Keyoung et al., (Nature biotechnology, 2001, pp. 843-850, p. 843, col. 1 last paragraph) teaches how the art has overcome the low selectivity of stem cell populations under cell surface enzymatic makers by transfecting cells with GFP placed under the regulatory control of cell-specific promoter (e.g., musashi, nestin) and isolating the transfectants by FACS. Moreover, the author teaches that by infecting dissociated neuronal progenitor cells with adenoviruses encoding GFP placed under th regulatory control of cell-specific promoters identified and isolated neuronal cells could be propagated after their virtual purification for over six months (p. 848, col. 2, last paragraph). The as-filed specification corroborates the lack of predictability of using any marker other than fluorescence markers for visualization of ES-derived cardiac cells when it states that in "an enzymatic reaction, detection sensitivity is relatively high, and a level of expression of a LacZ gene necessary for detection may be very low, but in order to visualize or isolate a cell while living, a LacZ gene cannot be used as a marker gene. For this reason, it is general to use an EGFP gene as a marker gene for such the purpose" (p. 20, paragraph 2). Applicant only provides factual data for the visualized mouse ES cell-derived cardiomyocytes using a fluorescent marker

gene (e.g., EGFP). Thus the art teaches the criticality of tissue-specific Nkx2.5 gene promoter in mouse ES cell-derived cardiomyocytes, and that markers other than fluorescent marker are unpredictable for sufficient visualization of a mouse ES cell-derived cardiomyocytes population.

As set forth above by the nature of the invention, the state of the prior art, neither the prior art of record nor the as-filed specification provides sufficient guidance to enable a person skilled in the art to employ cells other than mouse embryo-derived cardiac cells transfected with (i) a first DNA construct encoding **a fluorescence gene marker** operably linked to a strong constitutive CA promoter, wherein the DNA encoding said marker gene is separated from said promoter by a sequence of DNA which prevents transcriptional control by said promoter over the DNA encoding the marker gene, and (ii) a second DNA construct comprising a DNA encoding a recombinase-expressing gene operably linked to a second Nkx2.5 gene promoter, wherein said recombinase is capable of removing the sequence of DNA preventing transcriptional control in the first DNA construct in the methods as claimed . Thus the as-filed specification and state of the art exclusive teach differentiation of mouse stem cells into a germ line. . With respect to the use of any gene marker, it is unclear how a selective marker other than a light emitting protein can be used to visualize living target cells particularly because markers that required enzymatic reactions are very sensitive and thus expression of said marker very low and no sufficient to be visualized. Thus it would require an undue experimentation for one skilled in the art to reasonably extrapolate from one species of fluorescent maker to other types of markers as broadly claimed. Hence given the unpredictability of the art and the lack of working example in the instant specification, particularly when taken with the lack of guidance in the specification, it

would have required undue experimentation to practice the instant method to identify an enormous number of methods as broadly or generically claimed, resulting in the identification of a method for selective isolation or visualization of any mammalian ES cell line other than cardiac muscle cells derived from mouse ES cells as broadly claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 11, 14-18, 21, 24, 27, 30, 33, 34 and 36 are rejected under 35 USC 103 as being unpatentable Vallier et al, (PNAS, 2001, 98:2467-2472) in view Ong et al., US Patent No: 6,777,235, Date or Patent Aug. 17, 2004) and further in view of Rybkin et al., (Biol. Chem., 15927-15934, 2003).

Vallier et., (PNAS, 2001, 98:2467-2472) teach a system for conditional gene expression in embryonic stem cells that relies on tamoxifen-dependent Cre recombinase-loxP site-mediated recombination and bicistronic gene-trap expression vectors that allow transgene expression from endogenous cellular promoters (Abstract). Specifically, Vallier discloses a method of gene trap for genes that are conditionally expressed in embryonic stem cell (ES) comprising the steps of : i) transforming cells with a first trap vector (e.g., *pGTEV-Cre-ER*) and ii) transfecting cells with a second reporter vector (e.g., *pCAG-lox-STOP-EGFP*) (p. 2467, Abstract), the expression of which is prevented by tandemly repeated stop-of-transcription sequences flanked by loxP sites. Quantification of EGFP-expressing cells was performed by FACS (p.2468, col. 1, paragraph 1). Moreover, Vallier et., discloses that human alkaline phosphatase (hAP) expression was shown to be regulated accurately by 4'hydroxy-tamoxifen. Thus cells are transfected with a trap vector comprising a Cre recombinase activated by a given condition (e.g. an exogenous estrogen analog 4'hydroxy-tamoxifen) which induces expression of reporter activity in the reporter vector (e.g., *EGFP,* and *Adh,* see Table 1, columns 5 and 6, respectively; *hAP*, see, p.2472, col. 1, paragraph 1). Additionally, Vallier et., teach the schematic structure of :

i) the bicistronic trap vector having a unit of the following genes linearly connected: a SA, a βgeo as a reporter gene, an IRES, **Cre**-RE and a stop signal, and

ii) the reporter vector having a unit of the following genes linearly connected:

a constitutively activated promoter (e.g., CAG), **a first loxP sequence**, a drug resistance gene (hygro), a stop sequence, **the second loxP** and the reporter gene (p. 248, col.1, paragraphs 2-4; p. 2469, col. 1, Fig B; p. 2472, col. 1 paragraph 2).

Moreover, Vallier et., teach that the trap vector (e.g., *pGTEV-Cre-ER)* is under control of a **constitutively expressed promoter after integration downstream of said promoter** (p. 2470, col. 1, last paragraph). Further, Vallier et., teach a kit including the first DNA construct and, a second DNA construct (col. 6, lines 30-34).

Vallier et., does not specifically teach tissue-specific dependent Cre recombinase-expression and function.

However, at the time the invention was made, Ong et al., is an exemplified prior art that teaches that it is routine or well –established in the art to use cell-type or tissue type restricted expression of certain promoters operatively associated with a recombinase gene in combination with a gene of interest that has been flanked by recombinase recognition sequences, wherein the recombinase is expressed under the control of the cell-type or tissue type specific promoter and when expressed results in the excision of the gene of interest. (See for example col. 10, lines 40-45). Moreover, in column 8, lines 10-40, Ong et al., discloses a list of tissue or cell specific promoters. Ong et al., teaches that invention may be used to identify tissue or cell type specific genes and cells are then screened for activity of the indicator which will occur in the cell or tissue type in which the promoter is functional in any animal from which embryonic stem (ES) cell lines may be obtained (col. 6, lines 48-62) Further, Ong et., teach a kit including the first DNA construct and, a second DNA construct (col. 6, lines 30-34). Additionally, Rybkin et al., (JBC 2003, 15927-15934) teach inducible swich from proliferation to differenciation of mouse ventricular myocardium by conditional expression of simian virus 40 large T-antigen (Tag) under the control of the early cardiac promoter Nkx2.5 and Cre-mediated recombination (p. 15927, col. 1, paragraph 1, p. 15928, col. 1, paragraph 4).

It would have been obvious for one of ordinary skill in the art to have employed any of the known specific cell-type or tissue- type promoters, as exemplified by the cited references, in the bicistronic trap vector taught by Vallier to replace the tamoxifen-dependent Cre inducible recombinase in order to conditionally express a functional recombinase in target cells differentiated from murine ES cells, particularly because Ong et al., teaches the advantage of using a cell-type or tissue type restricted promoter operably linked to a marker gene in order to screening cell or tissue specific genes in any animal from which ES cell lines may be obtained. Thus, one of ordinary skill in the art would have been motivated to have employed any of the known tissue-specific promoters, as exemplified by the cited references, in the vector taught by Vallier in order to selectivity isolate a target cell by expression of a fluorescence marker protein induced by a tissue-depending Cre inducible enzyme. Further, one of ordinary skill in the art would have been motivated to use a cardiac restricted promoters such as Nkx2.5 as taught by Rybkin to isolate a pure population of ES cell-derived myocytes particularly because said gene constitutes a hallmark of ES cell-differentiated cardiac cell. The manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology. Moreover, based on the detailed teachings of the Vallier and Behfar publications and the Ong patent and the high level of skill in the art of molecular cloning, the skilled artisan would have had a reasonable expectation of success in generating a method for selectively isolating or visualizing a target cell as claimed.

Claims 1-6, 8-34 and 36 are rejected under 35 USC 103 as being unpatentable Vallier et al, (PNAS, 2001, 98:2467-2472) or in view Ong et al., US Patent No: 6,777,235, Date or Patent Aug. 17, 2004) and Rybkin et al., (JBC 2003, 15927-15934) as applied to claims 1-8, 11, 14-18, 21, 24, 27, 30, 33, 34 and 36 above and further in view of Yamamote et al., (Oncogene 2002, 899-908).

The teachings of Vallier et., (PNAS, 2001, 98:2467-2472) and Ong et al., US Patent No: 6,777,235, Date or Patent Aug. 17, 2004) are outlined above.

Neither Vallier et., or Ong et al., teach the use of adenovirus vectors for transferring a gene.

However, at the time the invention was made, Yamamote et al., successfully demonstrate conditional expression of the HST-1/FGF-4 gene in the testis of mice using the Cre/lox system by administration of **Cre-expressing adenovirus** *in vivo* (p. 900, col. 1, paragraph 3).

It would have been obvious for one of ordinary skill in the art to have employed any of the known specific cell-type or tissue- type promoters, as exemplified by the cited references, in the bicistronic trap vector taught by Vallier to replace the tamoxifen-dependent Cre inducible recombinase in order to conditionally express a functional recombinase in target cells differentiated from murine ES cells, particularly because Ong et al., teaches the advantage of using a cell-type or tissue type restricted promoter operably linked to a marker gene in order to screening cell or tissue specific genes in any animal from which ES cell lines may be obtained. Further, one of ordinary skill in the art would have been motivated to use adenovirus carrying the Cre gene, particularly because Yamamote et al., teachs that when a sufficient amout of a Cre si

supplied provided by the adenovirus-carrying the Cre gene, the stuffer seqeunce is excised and the the HST-1/FGF-4 gene under the control of a CAG promoter is expressed. The manipulation of previously identified DNA fragments and cell transformation systems is within the ordinary level of skill in the art of molecular biology. Moreover, based on the detailed teachings of the Vallier and Yamamote publications and the Ong patent and the high level of skill in the art of molecular cloning, the skilled artisan would have had a reasonable expectation of success in generating a method for selectively isolating or visualizing a target cell using adenoviruses carrying vectors as claimed.

Conclusion

Claims 1-34 and 36 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria Leavitt whose telephone number is 571-272-1085. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

To aid in correlating any papers for this application, all further correspondence regarding his application should be directed to Group Art Unit 1636; Central Fax No. (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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